In This Issue

Cell

Tumor Suppressor Identity Unmasked

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It has long been suggested that the chromosomal region *1p36* encoded a tumor suppressor; however, the identity of this gene has remained a mystery. Now Bagchi et al. created mice with either fewer or extra copies of a 4.3 Mb region corresponding to human *1p36*. Whereas extra copies of this region triggered excessive tumor suppression, fewer copies rendered cells tumorigenic. The authors determined that the chromatin remodeling protein Chd5 encoded in this region is a tumor suppressor that controls proliferation, apoptosis, and senescence via the p19Arf/p53 pathway. Furthermore, *CHD5* maps to a region of *1p36* that is frequently deleted in human cancer.

Coming Soon to Heterochromatin near You: SHREC

PAGE 491

Heterochromatin possesses a remarkable ability to repress transcription and recombination across large chromosomal domains. However, the mechanism by which condensed heterochromatin prevents transcription remains unclear. Sugiyama et al. now report a multienzyme repressor complex named SHREC that affects heterochromatic transcriptional silencing. SHREC localizes throughout heterochromatin, thereby restricting the occupancy of transcriptional machinery. These analyses suggest that SHREC functions as a versatile effector complex that could be targeted to different loci via specialized recruitment mechanisms to assemble repressive higher-order chromatin structures.

Putting the Brakes on MAPK in the Cell Cycle

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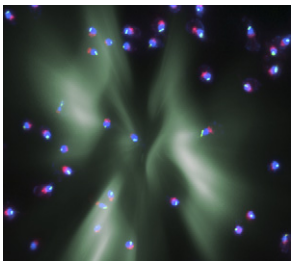
In budding yeast, mating pheromones trigger G1 arrest and cell differentiation via the MAP kinase (MAPK) pathway, but this signaling response is inactivated when cells begin a new division cycle. To gain insight into the mechanism of inactivation, Strickfaden et al. show that G1 CDKs phosphorylate the MAPK scaffold protein Ste5. This phosphorylation disrupts Ste5 recruitment to the plasma membrane, thereby inhibiting MAPK activation. While MAPK pathways are known to regulate the cell cycle, this is the first example showing that the reverse regulation is also important.



Monopolin-izing Aurora B Function in Meiosis

PAGE 477

Mis-segregation of chromosomes during meiosis is the leading cause of miscarriages and mental retardation in humans. Monje-Casas et al. investigate the mechanisms that ensure faithful segregation of chromosomes during meiosis in *S. cerevisiae*. The authors find that the protein kinase Aurora B regulates microtubule-kinetochore attachment during meiosis, promoting cosegregation of sister chromatids to the same spindle pole during meiosis I and their separation to opposite poles during meiosis II. Furthermore, they show that the monopolin complex, which is responsible for sister kinetochore co-orientation in meiosis I, links sister chromatids at centromeres and is sufficient to ensure that Aurora B promotes cosegregation of sister chromatids.

Coming together in Death (Domains)

PAGE 533

Proteins of the death domain superfamily mediate assembly of oligomeric signaling complexes important for the activation of caspases and kinases. Here Park et al. solve the crystal structure of the core of the caspase-2 activating complex PIDDosome, revealing an asymmetric complex comprised of seven and five death domains of RAIDD and PIDD, respectively. Despite the asymmetry, all death domains in the complex are in quasi-equivalent environments, with three types of interaction interfaces identified. The interactions identified here may represent a general mechanism of assembly in the death domain superfamily.

Microtubules Mind the Gaps

PAGE 547

Gap junctions are formed by the apposition of gap junction proteins on adjacent cells and are essential for maintaining a normal heart rhythm. Here Shaw et al. examine whether gap junctions proteins—connexons—are targeted to the plasma membrane in a random fashion or are more specifically directed to their correct location at cell-cell borders. The authors report the rapid and directed targeting of connexons to adherens junctions, or specific regions of cell-cell contact. This process involves microtubules, the microtubule plus-end-tracking protein EB1, and EB1-associated proteins that may tether microtubules to adherens junctions as cortical anchors at the cell-cell border.

LSD1 Trips Nuclear Receptor Activation

PAGE 505

Nuclear receptors undergo ligand-dependent conformational changes required for corepressor-coactivator exchange; however, whether specific histone marks impose ligand dependency for gene activation is unknown. Garcia-Bassets et al. report that inhibitory histone methylation prevents unliganded nuclear receptors from binding to their target gene promoters and causing constitutive gene activation. This strategy imposes a requirement for specific histone demethylases, including LSD1, to permit ligand-dependent activation of gene expression. The data therefore suggest a link between the histone code and ligand-induced transcriptional control.

The Mechanics of Cell Migration

PAGE 561

Cells move via cycles of leading edge protrusion, adhesion, and retraction. Giannone et al. study the coordination of these processes and present evidence that myosin II pulls the rear of the lamellipodial actin network, causing upward bending, edge retraction, and initiation of new adhesion sites. The actin network then separates from the edge and condenses over the myosin. Protrusion resumes as lamellipodial actin regenerates from the front and extends rearward until it reaches newly assembled myosin, initiating the next cycle. Thus, actin polymerization periodically builds a mechanical link, the lamellipodium, connecting myosin motors with the initiation of adhesion sites, suggesting that the major functions driving motility are coordinated by a biomechanical process.

Preventing Pregnancy-Induced Cardiomyopathy

PAGE 589

Postpartum cardiomyopathy (PPCM) is associated with severe heart failure after pregnancy and is considered among the leading causes of death in postpartum women in industrialized countries. Hilfiker-Kleiner et al. now show that PPCM can be induced in mice by the absence of cardiomyocyte STAT3 activity. Myocardial cells lacking STAT3 exhibit enhanced oxidative stress, leading to the release of cathepsin D, a protease that cleaves the hormone prolactin. Cleaved prolactin induces cardiac endothelial cell apoptosis and promotes PPCM. Bromocriptine, an inhibitor of prolactin release, prevents PPCM by reducing circulating prolactin in STAT3-deficient mice, thereby providing a potential treatment for women at high risk for PPCM.

A New Factor in Insulin Secretion

PAGE 577

Insulin signaling pathways regulate growth and metabolism in mammals and invertebrates in response to nutrient availability. Defects in insulin signaling are associated with diabetes and other serious metabolic diseases. Here Kao et al. have identified a new modulator of insulin secretion, the ATPase ASNA-1. In *C. elegans,* the lack of *asna-1* function promotes growth arrest. In mammals, ASNA-1 is expressed in pancreatic beta-cells and modulates insulin secretion. Human ASNA-1 can substitute for the *C. elegans* gene, suggesting that ASNA-1 function has been strongly conserved in evolution.

Tuning in the Noise in Odorant Sensing

PAGE 601

How inputs from different classes of odorant receptor neurons (ORNs) are processed is an intensely studied question. In flies, synaptic connections between ORNs and their downstream synaptic partner projection neurons (PNs) are one-to-one, yet PNs are more broadly tuned to odors than ORNs. Here Shang et al. discover an unexpected source of crosstalk between odorant receptors—excitatory local circuits. Lateral excitation may add background "noise," boosting PN signals and enhancing their transmission to third-order neurons. Benefits of noise on information transmission are known in physics as "stochastic resonance." Although this phenomenon has been suggested to play a role in the brain, this may be the first empirical example of a circuit that is "noisy" by design.

Folding under Evolutionary Pressure

PAGE 613

The folding of most small, naturally occurring proteins occurs with highly cooperative transitions and smooth free energy landscapes, and thus non-native states are generally not observed. Here Watters et al. examine whether the same is also true for Top7, the first computationally designed stable protein that lacks an evolutionary history. Experimental characterization reveals that Top7 folding is much more complex than folding of similarly sized naturally occurring proteins. By demonstrating that cooperative folding is not a general property of a polypeptide chain that can fold to a native structure, the results support the hypothesis that these characteristics are a result of natural selection. Furthermore, the results may have significant implications for engineering proteins for use in vivo.